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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,697	01/30/2002	Donald W. Petersen	048057/275988	8553

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EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/060,697	PETERSEN, DONALD W.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Initially, Applicants are requested to note that the Examiner for this application has changed, future correspondence should be directed to Allison Ford, Art Unit 1651, whose contact information can be found below.

For purposes of clarity, the most recent prosecution history of this application is briefly summarized:

Claims 16-30 are pending in the current application.

All claims were finally rejected in an office action mailed 15 June 2004 under 35 USC 103(a) as being obvious over the teachings of O'Leary et al (US Patent 5,484,601), Yim et al (US Patent 5,385,887) and Wironen et al (WO 98/40113), taken as a whole.

Applicants appealed the rejection to the Board of Patent Appeals and Interferences, providing an Appeal Brief on 11 April 2005.

The Examiner's Answer, mailed 28 June 2005, added a new grounds of obviousness-type double patenting rejection over the claims, in light of the claims of US Patent 6,652,887 and the claims of US Application No. 09/327,761, each in view of Wironen et al (WO 98/40113), and over the claims of US Application No. 09/947,833. Applicants noted the new grounds of rejection in the Reply Brief received 9 November 2005.

The Board of Patent Appeals and Interferences provided a decision on 7 December 2006 (Appeal No. 2006-0704). The Examiner was affirmed in part. The Board affirmed the obviousness-type double patenting rejections, but reversed the sole obviousness rejection.

In light of the Board decision, Applicants have requested reconsideration of the application. This request, received 29 January 2007, is granted; the finality of the rejections of record is withdrawn; however new grounds of rejection have been set forth below. 37 CFR 1.198 provides that when a

decision by the Board of Patent Appeals and Interferences on appeal has become final for judicial review, prosecution of the proceeding before the primary examiner will not be reopened or reconsidered by the primary examiner except under the provisions of § 1.114 or § 41.50 of this title without the written authority of the Director, and then only for the consideration of matters not already adjudicated, sufficient cause being shown. MPEP 1214.03 states that if the examiner has specific knowledge of the existence of a particular reference or references which indicate non-patentability of any of the appealed claims as to which the examiner was reversed, he or she should submit the matter to the Technology Center (TC) Director for authorization to reopen prosecution under 37 CFR 1.198 for the purpose of entering the new rejection. Claims 16-30 have been considered on the merits. The TC Director's approval is indicated at the end of this action reopening prosecution.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary et al (US Patent 5,484,601), in view of Yim et al (US Patent 5,385,887), Sottosanti (US Patent 5,366,507), Hanker et al (US Patent 4,619,655), Snyders, Jr (US Patent 5,425,769) and Wironen et al (WO 98/40113).

Applicants' claims are directed to a bone graft substitute composition that generally comprises (a) calcium sulfate; (b) demineralized bone matrix; (c) cancellous bone; (d) a plasticizing substance; and (e) a mixing solution; wherein the cancellous bone has a particle size between about 1 and about 4 mm. Some

claims further define the specific mixing solution, the plasticizing substance, and the calcium sulfate (specifically as calcium sulfate hemihydrate), and the proportion (w/w) of each component.

At the time the invention was made, numerous bone graft substitute materials were known in the art. One such bone graft substitute material is described by O'Leary et al. Specifically O'Leary et al disclose a 'flowable' demineralized bone powder composition, comprising demineralized bone powder and a biocompatible liquid synthetic organic material as a carrier (which applicants call a mixing solution); optionally, thixotropic agents, medicaments and the like can further be included (See O'Leary et al, col. 1, ln 36-43). Still further, O'Leary et al. disclose that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements, parenchymal cells, growth factors, bone morphogenic proteins, and mesenchymal elements (See O'Leary et al, col. 2, line 53-col. 3, line 13). The bone powder is preferably provided in an amount equaling from about 5 to about 80 weight percent, more preferably from about 20 to about 60 weight percent (See O'Leary et al, col. 4, ln 18-22). O'Leary et al disclose glycerol as being a preferred carrier/suspension liquid; however, they further state that due to the natural tendency of the demineralized bone powder to separate when provided in glycerol, it is desirable to include thickeners (thixotropic agents), including carboxy methylcellulose (which applicants calls both a plasticizing substance and a cellulose derivative), to improve the suspension-keeping characteristics of the composition (See O'Leary et al, col. 3, ln 55-col. 4, ln 6). It is noted that O'Leary et al defines 'flowable' as a consistency ranging from 'readily deformable' (e.g. putty-like) to 'runny' (See O'Leary et al col. 3, ln 30-36); thus the bone graft substitute material of O'Leary et al can be formed into, and provided as, a putty.

Therefore, O'Leary et al. provides the disclosure to produce a bone graft substitute composition containing a demineralized bone powder, a thixotropic agent, such as carboxymethyl cellulose (which is a cellulose derivative, and thus a plasticizing substance, as defined by the specification), and a mixing solution. O'Leary teaches that this bone graft substitute may be prepared in multiple forms from liquid to

paste-like depending upon the requirements of the practitioner. O'Leary et al does not disclose the inclusion of calcium sulfate in their bone graft substitute composition.

However, while O'Leary et al do not include the currently claimed elements of calcium sulfate or cancellous bone in their bone graft composition, it is noted that the O'Leary patent clearly teaches that "any variety of substances" can be introduced to the composition include "inorganic elements," and it is submitted that both calcium sulfate and cancellous bone were known osteoconductive and/or osteoinductive elements which were routinely included in bone graft substitute compositions specifically for these and other beneficial properties. Therefore, it would have been obvious to one of ordinary skill in the art to add each of calcium sulfate and cancellous bone to the bone graft substitute composition of O'Leary et al because, at the time the invention was made.

With regards to addition of calcium sulfate, calcium sulfate was known to be a beneficial and useful component in bone grafting materials, for example, see Yim et al: Yim et al disclose a bone substitute material useful for delivering osteogenic proteins comprising calcium sulfate hemihydrate and cellulose materials, including cellulose derivatives. Yim et al report the calcium sulfate hemihydrate improves osteoconduction, and improves the moldability of the material (See Yim et al, col. 7, ln 50-65). The cellulose derivatives, which include carboxymethyl cellulose, aid in sequestering the proteins at the implant site so as to enhance their effectiveness (See Yim et al, col. 7, ln 26-49).

Additionally, at the time the invention was made, the use of both calcium sulfate and demineralized bone matrix together in bone grafting materials was known, see Sottosanti, Hanker et al, and Snyder, Jr: Sottosanti et al disclose a bone graft composite material comprising demineralized, freeze-dried, allogenic bone (DFDBA) and calcium sulfate (See Sottosanti et al, col. 2, ln 24-26); Hanker et al disclose mixing demineralized freeze-dried bone with Plaster of Paris (from calcium sulfate hemihydrate) (See Hanker et al, col. 2, ln 24-25); and Snyders, Jr disclose a composition comprising collagen, plaster

(from calcium sulfate hemihydrate + sterile water), and demineralized bone matrix as having osteoinductive capabilities (See Snyders, Jr, col. 3, ln 51-54; col. 4, ln 1-5; and col. 5, ln 42-43).

Based on the abundance of teachings in the art regarding the benefits of calcium sulfate, both individually and in combination with demineralized bone matrix, in bone grafting compositions, it would have been obvious to one of ordinary skill in the art to include calcium sulfate in the composition of O'Leary et al. Additionally, though not explicitly stated, because calcium sulfate is naturally a powder, it would be necessary to add an aqueous solvent to the bone grafting material in order to hydrate and activate the calcium sulfate to a workable consistency; one of ordinary skill in the art would be aware such a solution would be necessary and the selection and use of either sterile water or saline or other buffers is deemed conventional and well within the skill of the practitioner (thus a mixing solution would inherently be recognized as necessary, and thus provided, in any bone graft composition comprising calcium sulfate).

Beyond the added osteogenic properties that calcium sulfate provides, additional motivation for including calcium sulfate in the composition of O'Leary et al can be derived from the recognized deficiencies of the composition of O'Leary et al, as recognized by Wironen et al. Specifically, in their review of the available bone graft materials, Wironen et al disclose deficiencies with the bone substitute material of O'Leary et al (commercially available as GRAFTON®). Wironen et al note that because glycerol (which is used as the suspension/carrier material in GRAFTON®) is water soluble, it was considered likely that the glycerol (along with the demineralized bone powder) would prematurely wash away from the implantation site (See Wironen et al, Pg 3). In view of this concern, one of ordinary skill in the art would have been motivated to utilize calcium sulfate as a carrier/scaffold material in the material of O'Leary et al in place of the glycerol, as calcium sulfate was recognized as a mechanically strong (i.e. does not wash away in presence of body fluid), yet totally resorbable material that is particularly suited for use in bone substitute materials. Calcium sulfate is resorbed by the body in a

period of approximately 4-20 weeks, which approximately correlates with the time period for new bone formation (See Snyders, Jr, col. 4, ln 57-68). Clearly, dissolution of the scaffold material at a rate approximately equal to that of new bone formation is desirable, as it would permit natural bone regeneration on the natural timescale. One would have a reasonable expectation of successfully including the calcium sulfate hemihydrate as a scaffold/carrier material for the bone graft substitute material of O'Leary et al because use of calcium sulfate hemihydrate in combination with the bone graft material of O'Leary et al, because use of both calcium sulfate (including calcium sulfate hemihydrate) and demineralized bone matrix in a single grafting material was well established in the art (See Sottosanti, Hanker et al, & Snyders, Jr).

With regards to addition of cancellous bone, it is submitted that cancellous bone was also known to be a beneficial and useful component in bone grafting materials, for example, see Wironen et al: Wironen et al disclose a bone paste which is useful for filling osseous defects, comprising an osteogenic component, such as demineralized bone matrix, suspended in a hydrogel carrier, and optional ingredients such as carboxymethyl cellulose, wetting agents and growth factors (BMPs) (See Wironen et al, Pg. 5-6). Wironen et al further disclose their composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)" (See Wironen et al, Pg 13). The size of the bone chips can be in the range of 80 um to 10 mm (See Wironen et al, Pg. 13).

Therefore, bone chips, including cancellous bone chips, provide osteogenic proteins (BMPs) which are inherently contained within natural bone, as well as structural bulk and support. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further

include cancellous bone chips, within the range claimed, into the composition of O'Leary et al and/or into the composition of O'Leary et al, as modified to comprise calcium sulfate hemihydrate, for the benefit described in the disclosure of Wironen et al, i.e. they fill larger bone voids and provide an added spectrum of biological properties to the composition. With regards to the quantity and size of cancellous bone chips included in any bone graft composition, it is submitted that because Wironen et al teach the cancellous bone is included for the express purpose of filling larger bone voids, the quantity and size of cancellous bone chips used would depend directly on the size and shape of the void to be filled, and thus would be routinely optimized by the artisan of ordinary skill without undue experimentation.

It is clear that the components as claimed are all well known to be included in bone graft compositions. The prior art clearly indicates that demineralized bone matrix is conventionally included in a moldable bone graft composition for the purpose of acting as an osteoinductive agent by delivering bone morphogenic proteins to the area of the desired bone graft. It is also clear that the addition of calcium sulfate hemihydrate, an inorganic compound that becomes moldable when wetted and then ultimately hardens, is both well known and imparts multiple beneficial properties to moldable bone grafts, the benefits including enhancement of osteoconductive property of the composition, as well as providing a supporting structure which degrades at substantially the same rate as new bone growth. It is also clear that plasticizing substances such as those claimed are known to be used in prior art moldable bone graft compositions expressly for the purpose of improving the moldability of the composition. Finally, it is clear that it is conventional to include cancellous bone into moldable bone graft compositions for the benefit of both osteo-induction and as providing bulk in compositions intended to fill larger bone voids. Appellants are claiming conventional bone graft composition comprising conventional ingredients, combined in a conventional manner, and in known amounts. Further, the state of the art of these components are so well known that optimization of amounts for the purpose of changing the both the

flowable and "set-up time" properties of the composition are deemed well within the skill of the practitioner. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

With regards to the obviousness-type double patenting rejection: is noted Applicants have submitted acceptable terminal disclaimers against each of the commonly owned US Patents or patent applications, and thus the rejections/provisional rejections are withdrawn.

With regards to the obviousness rejection: The arguments of Applicants provided in the Appeal Brief of 11 April 2005, which were affirmed by the Board of Patent Appeals and Interferences, were based on the idea that one of ordinary skill in the art would not have been motivated to combine the teachings of O'Leary et al and Yim et al, otherwise stated, one would not be motivated to add calcium sulfate (as disclosed by Yim et al) to the composition of O'Leary et al, in order to improve handling, moldability or consistency properties of the composition of O'Leary et al. It was set forth that because O'Leary et al does not suggest their composition suffers from poor handling, moldability, or consistency, and because it is not clear from the disclosure of Yim et al that calcium sulfate hemihydrate is even capable of imparting such properties to any composition, motivation based on such is inappropriate and does not support a *prima facie* case of obviousness. Additionally, Applicants argue that one of ordinary skill in the art would not have been further motivated to combine the teachings of Wironen et al with either of the compositions or teachings of O'Leary et al or Yim et al. Applicants argue that Wironen et al is concerned with a cross-linkable gelatinous composition that is thermoreversible; Applicants argue that Wironen et al can only be relied upon to show that cancellous bone chips can be contained in the specific gelatin composition.

The arguments and opinion of the Board have been fully considered, and in light of such, the rejection of record has been modified. However, the claims stand rejected under the idea that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to add a calcium sulfate component, particularly calcium sulfate hemihydrate, as well as cancellous bone chips to the composition of O'Leary et al. The new grounds of rejection attempts to better explain the state of the art, and the knowledge of the artisan in the field of bone grafting and tissue engineering, as such must be taken into consideration in determining obviousness, See *Graham v. John Deere Co.* 383 US 1, 17-18, 148 USPQ 459, 467 (1966) & *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). With regards to the obviousness of adding calcium sulfate to the composition of O'Leary et al: as set forth in the rejection above, numerous bone grafting composition materials were known in the art, certain components were generally known to be routinely used due to their known osteoconductive and/or osteoinductive properties, including both demineralized bone matrix and calcium sulfate (See, e.g., Sottosanti, Hanker et al, Snyders, Jr, Gertzman et al). When the full scope of teachings of the prior art is taken into consideration, it is clear that calcium sulfate is not merely just a 'set-up agent' that affects consistency and moldability of a composition, but rather was recognized as an osteoconductive material. For example, Snyder et al discloses calcium sulfate "not only does not inhibit the normal growth and healing process of bone, it also has been characterized as an accelerant of the same because of its contribution of calcium ions to the process [of bone growth and healing]." (Snyders, Jr, col. 4, ln 64-68); in fact, each of the cited references recognize the osteoconductive properties of calcium sulfate. Therefore, one of ordinary skill in the art would have been motivated to add calcium sulfate to the composition of O'Leary et al, not because the potential effect on set-up time, but rather in order to improve the osteoconductive properties of the final bone graft substitute material.

Furthermore, while improving the osteoconductive properties of the final material is considered, by itself, to be sufficient motivation to add calcium sulfate to the O'Leary et al composition, it has been further set forth that at the time the invention was made certain deficiencies were noted in the composition of O'Leary et al, specifically the poor ability of the glycerol carrier solution to retain the demineralized bone at the implant site, use of a calcium sulfate carrier material would overcome this deficiency as calcium sulfate degrades at a rate approximately equal to that of new bone formation. Thus, one would be further motivated to utilized calcium sulfate in the composition of O'Leary et al in order to correct for the recognized deficiency associated with the glycerol carrier material.

Still further, in response to Applicants' arguments regarding the non-obviousness of including cancellous bone chips (as disclosed by Wironen et al) in the composition of O'Leary et al, Applicants' argument that Wironen et al only suggests cancellous bone chips can be provided in their specific gelatinous composition are not found persuasive. Merely because Wironen et al discloses the bone chips can be provided in their hydrogel matrix does not suggest that bone chip cannot be provided in other solutions, nor that inclusion of bone chips in other compositions would not provide the same benefits (provision of various osteogenic (osteoinductive) properties, as well as provide structural bulk and support in graft compositions intended to fill large bone voids). Use of bone chips, including cancellous bone chips, in other carrier vehicles, and even in combination with both calcium sulfate and demineralized bone matrix is well known in the art, see e.g. Sottosanti at col. 4, ln 6-24. Therefore, absent objective evidence that cancellous bone chips would *not* provide their known benefits when provided in the suggested combination, the rejection of record stands.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
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Art Unit 1651

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